DETAILED ACTION

Upon review of the Final rejection mailed May 2, 2011, it was noted that the action contained some inadvertent omissions. Therefore, this supplemental action is created to ameliorate deficiencies in the previous action.

Claim Objections

Claim 75 is objected to because of the following informalities: an article is missing between "express" and "P2". Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 75-79, 81, 82 and 86-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kontani et al. (Cancer Gene Therapy. 2002; 9: 330-337), Kikuchi et al. (Blood. 2000; 96 (1): 91-99) and Krug et al. (European Journal of Immunology. 2001; 31: 3026-3037).

Kontani et al. teach a nucleotide vaccine composition comprising a mixture (top of first column on page 332) of a plasmid encoding an antigen, MUC1 (see "plasmid DNA" on page 331) and a subclass of antigen-presenting dendritic cells (see Preparation of DCs on page 331) and the top of page 332 describing the "combination of DNA and DC's". The nucleotide sequence of Kontani et al. is produced by cloning nucleotide sequence encoding an MHC-binding protein into a vector and propagated in a tumor cell line, see "Plasmid DNA" and

Transfection of MUC1 cDNA..." on page 331. The antigen-presenting cells of Kontani et al. are generated by isolating antigen-presenting cells from a subject, see "Preparation of DCs" on page 331. Although Kontani et al. do not pre-incubate the plasmid and the dendritic cells together, Kontani et al. certainly suggest the benefits of doing so since antitumor immunity was enhanced upon simultaneous administration at the same site, see the last two paragraphs of the discussion section bridging pages 335-336. Kontani et al. teach producing an immune response by administering the vaccine composition, see the paragraph bridging pages 331-332.

Kontani et al. do not teach or suggest modifying a plasmacytoid dendritic cell to express CD40L or adding an unmethylated CpG sequence to a nucleic acid sequence encoding the tumor antigen of Kontani et al.

Kikuchi et al. teach modifying dendritic cells to express CD40L, see "cytokines" on page 92.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify dendritic cells to express CD40L to enhance T-cell activation and anti-tumor antigen presentation, see Figure 8 on page 96, the paragraph bridging the columns on page 97 and "Dendritic cell-based cancer immunotherapy" bridging pages 97-98.

Neither Kikuchi et al. nor Kontani et al. teach or suggest modifying a plasmacytoid-type dendritic cell or adding an unmethylated CpG sequence to a nucleic acid sequence encoding the tumor antigen.

However, Krug et al. teach toll-like receptors on plasmacytoid dendritic cells are required for recognition of CpG motifs, see Krug et al. also specifically demonstrate that synergistic

activation of plasmacytoid dendritic cells, stimulating the production of IL-12, IFN-α and bioactive IL-12 p70, see section 2.4 and Figures 5 and 9.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the plasmacytoid dendritic cells of Krug et al. to express CD40L and to add the CpG motif to the nucleotide antigen vaccine of Kontani et al. to induce a synergistic activation of PDCs for production of IL-12. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for inducing synergistic activation of PDCs in the presence of CD40L and a CpG nucleotide motif since Krug et al. specifically teach that toll-like receptors present on PDCs are responsible for recognition of CpG motifs and that synergistic activation of PDC's is accomplished through simultaneous presence of CD40L and CpG nucleic acids. One of ordinary skill in the art at the time the invention was made would have had further reasonable expectation of success for modifying PDC's to express CD40L since Kikuchi et al. demonstrate successful expression of CD40L on dendritic cells.

Applicant states that Kontani et al. differs from the instant invention since the two constituents of Kontani et al. are administered as separate injections.

Applicant's arguments have been fully considered, but are found unpersuasive. Kontani et al. explicitly teach that the DNA and dendritic cells were administered simultaneously at the same site, see the paragraph above the "Materials and Methods" section on page 331 and the very top of page 332. Therefore, even though the two components of Kontani et al. are administered separately, they are administered at the same time and at the same site, which at least suggests a vaccine mixture *in situ*.

Applicant also points out the limitations not taught by Kontani et al., now recited in newly presented independent claims.

However, the limitations not taught by Kontani et al. are taught by other references used in combination with the teachings of Kontani et al.

Applicant points to Figure 3 of Kontani et al. and asserts that the vaccine composition only induces a prophylactic response and not a therapeutic one. Applicant also points to Figure 4 of Kontani et al. and asserts that when the vaccine composition of Kontani et al. is administered after tumor challenge, the tumors were still growing in the test animals, although at a reduced rate.

Figures 3 and 4 of Kontani et al. in view of applicant's arguments have been fully considered, but are found unpersuasive for several reasons. Regarding the data presented by Kontani et al. in Figure 3, the inoculant administered by Kontani et al. is outside the scope of the instant claims since only DNA is administered and not DNA in combination with dendritic cells. Second, even if the inoculant of Kontani et al. is within the instant scope of the claims, the composition administered by Kontani et al. is within the scope of the conventional definition of vaccine provided in the instant disclosure in paragraph [0115] (emphasis added):

[0115] The vaccine composition of the invention can be employed for eliminating pre-existing tumors or pathogens, for treating cancer or an infectious disease. However, **the vaccine composition can** also or **alternatively be used to protect a subject, preferably a mammalian subject and more preferably a human subject, against disease encounter or protect against a challenge or relapse with tumor cells** or the pathogenic infectious agent (microorganism). **In such a case, the vaccine is used for preventing cancer or an infectious disease, for example, having prophylactic properties.**

Therefore, according to the instant disclosure, "vaccine" encompasses ameliorative and/or prophylactic effects. Therefore, suppression of tumor growth, as clearly depicted by Kontani et al. in Figure 4, or prevention, i.e. producing a prophylactic response, as also demonstrated by Kontani et al. is within the scope of the instant "vaccine" composition.

Applicant further contrasts the instant invention with that of Kontani et al. by pointing out that 100% of the animals survived when the instant vaccine is administered, compared with only a 20% survival rate shown by Kontani et al.

Applicant's arguments have been fully considered. While the instant results are encouraging, the instant claims are drawn to a nucleotide vaccine composition mixture comprising at least two components. The teachings of Kontani et al., Kikuchi et al. and Krug et al. teach all of the instantly required ingredients within the vaccine composition and provide motivation for combining various elements with a reasonable expectation of success. The formulation of Kontani et al. does not possess all of the instantly required limitations within the vaccine composition, but is supplemented by the teachings of Kikuchi et al. and Krug et al. It is reiterated that the vaccine of Kontani et al. prevented tumor growth, see Figures 1 and 2, and also suppressed tumor growth, see Figure 4. These results clearly indicate that the composition of Kontani et al. metes the criteria for qualification as a vaccine.

With respect to the teachings of Kikuchi et al., applicant asserts that animal survival is only achievable when the vaccine is directly injected into the tumors. Applicant points out that intratumor vaccination is not practical for humans and animals.

Applicant's arguments have been fully considered, but are found unpersuasive since the instant claims are drawn to a composition and not a method. Therefore, the precise method of administration is not relevant to the instant claims.

Applicant states that one of ordinary skill in the art at the time the invention was made would not have combined the teachings of Kikuchi et al. and Kontani et al. to induce tumor specific immunity against tumor re-challenge based on poor survival rates. Applicant also states that the ordinary artisan would not expect systemic and therapeutic immunity to eliminate existing tumors and prevent against tumor re-challenge.

Applicant's arguments and a review of Kikuchi et al. and Kontani et al. have been fully considered, but are found unpersuasive. The instant claims require a vaccine comprising two components. The vaccine, according to the definition provided in the disclosure in paragraph [0115], encompasses prophylactic properties. The vaccine composition of Kontani et al. comprises DNA and dendritic cells administered simultaneously at the same site, which induces a protective immune response upon tumor challenge, see Figures 1 and 2. The data presented by Kontani et al. are also clearly induce therapeutic efficacy as evidenced by the data presented in Figure 4.

Applicant states that the teachings of Krug et al. show CD40L and CpG oligonucleotides being added to a culture solution containing plasmacytoid dendritic cells in section 2.1 and points out that the CpG oligonucleotides are not provided as part of a vector.

Applicant's arguments and a review of Krug et al. have been fully considered, but are found unpersuasive. Krug et al. teach toll-like receptors on plasmacytoid dendritic cells are required for recognition of CpG motifs, see Krug et al. also specifically demonstrate that

synergistic activation of plasmacytoid dendritic cells, stimulating the production of IL-12, IFN-α and bioactive IL-12 p70, see section 2.4 and Figures 5 and 9.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the plasmacytoid dendritic cells of Krug et al. to express CD40L and to add the CpG motif to the nucleotide antigen vaccine of Kontani et al. to induce a synergistic activation of PDCs for production of IL-12. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for inducing synergistic activation of PDCs in the presence of CD40L and a CpG nucleotide motif since Krug et al. specifically teach that toll-like receptors present on PDCs are responsible for recognition of CpG motifs and that synergistic activation of PDC's is accomplished through simultaneous presence of CD40L and CpG nucleic acids. One of ordinary skill in the art at the time the invention was made would have had further reasonable expectation of success for modifying PDC's to express CD40L since Kikuchi et al. demonstrate successful expression of CD40L on dendritic cells. Therefore, the combination of Krug et al., Kontani et al. and Kikuchi et al. teach all of the limitations required by the instant claims and provide motivation for modifying the references with a reasonable expectation of success.

Applicant also argues that Krug et al. is not in the same field of endeavor as Kontani et al. and Kikuchi et al. Applicant asserts that one of ordinary skill in the art would not combine the teachings of intracellular pathogens with an anti-tumor composition.

Applicant's arguments have been fully considered, but are found unpersuasive since even some viruses are known to establish tumors and cancers. Also, the impetus of developing anti-tumor or anti-pathogenic compositions is to boost and/or enhance the immune system against

pathogenic antigens. Therefore, all of the references, Kontani et al., Kikuchi et al. and Krug et al. are in the same field of endeavor.

Claim 80 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kontani et al., Kikuchi et al. and Krug et al. as applied to claims 75-79, 81, 82 and 86-90 above, and further in view of Ni et al. (Journal of Biological Chemistry. 2002; 277 (15): 12689-12696).

See the teachings of Kontani et al., Kikuchi et al. and Krug et al. above. None of the references teach or suggest antigen-presenting cells expressing a P2 receptor.

However, Ni et al. teach dendritic cells nucleotide receptors from the P2X family, see Figure 5.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate a PX2 receptor in a dendritic cell with a reasonable expectation of success in the vaccine composition of Kontani et al., Kukichi et al. and Krug et al. to enhance DC activation, see page 12693 of Ni et al.

Claim 83 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kontani et al., Kikuchi et al. and Krug et al. as applied to claims 75-79, 81, 82 and 86-90 above, and further in view of Fritz et al. (WO 02/069900).

See the teachings of Kontani et al., Kikuchi et al. and Krug et al. above. None of the references teach or suggest SEQ ID NO: 5.

However, Fritz et al. teach a sequence comprising instant SEQ ID NO: 5, see the sequence alignment provided below:

Query Match 100.0%; Score 47; DB 1; Length 21;
Best Local Similarity 100.0%;

Matches 9; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 AFHGDAEAL 9
||||||||||
Db 5 AFHGDAEAL 13

One of ordinary skill in the art at the time the invention was made would have been motivated to use the fusion protein sequence of Fritz et al. with a reasonable expectation of success in the vaccine composition of Kontani et al., Kukichi et al. and Krug et al. to treat cancer, see claim 29 of Fritz et al.

Allowable Subject Matter

Claims 84 and 85 are allowed. The prior art does not teach or suggest SEQ ID NOs 3 or 4.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHANON A. FOLEY whose telephone number is (571)272-0898. The examiner can normally be reached on flex, generally M-F 7AM - 3 PM, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on (571) 272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SHANON A. FOLEY/
Primary Examiner
Art Unit 1648